REMARKS

Applicants herein cancel claims 29-34, 37, and 39-40 without prejudice. Applicants also amend claims 25-28, 35, and 36 and add new claims 41-52, to more particularly set forth the claimed methods. Applicants submit that the amendments do not add new subject matter. Specifically, support for new and amended claims is found, for example, at page 25, lines 5-7 and 15-18 (stringent hybridization conditions); page 45, lines 1-7 (promoting the survival of neuronal cells); and page 46, lines 1-3 (inducing neurite formation from neuronal cells). New claims 41-52 relate to methods comprising administering BMP-11 polypeptides comprising specific amino acid sequences and omit hybridizing and functional limitations that are subject to rejections under 35 U.S.C. § 112. The specified methods and polypeptides do not expand the scope of previously examined claim limitations.

The amended claims are submitted in response to a telephonic interview with the Examiner to discuss the entry of an amendment of the claims after final, as well as to discuss hybridization and functional limitations relating to BMP-11 polypeptides used in the instant methods. Applicants thank the Examiner for discussing the new claims. As decided in the interview, the Applicants file a request for continued examination with this paper, and present argument below regarding the enablement of the claimed nucleotide sequences that hybridize under stringent conditions.

After entry of this amendment, claims 25-28, 35, 36, 38, and 41-52 will be pending. The Applicants are pleased that the instant claims are not rejected on novelty or obviousness grounds, and note that the claims stand rejected under 35 U.S.C. § 112, as well as on obviousness-type double patenting grounds.

Maintained Rejection of Claims 29-36 and 38-40 under 35 U.S.C. § 112

The Examiner maintains the rejection of claims 29-36 and 38-40 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled for the full scope of the claimed methods of inducing neuronal cell differentiation from a progenitor cell or of modulating proliferation of neuronal cells.

As discussed in the telephonic interview, Applicants cancel claims 29-34, 39 and 40 and amend claims 35, 36, and 38 to depend from claims 25- 28, which are not subject to this rejection, solely to expedite prosecution of this application and without acquiescing to the Examiner's grounds for rejection. Applicants expressly reserve the right to pursue the canceled subject matter in another application. Applicants submit that the maintained enablement rejection set forth at pages 2-9 of the Office Action is now moot, and request that it be reconsidered and withdrawn.

New Rejections Under 35 U.S.C. § 112

A. Written Description

The Examiner's rejection of claims 33 and 34 under 35 U.S.C. § 112, first paragraph, as allegedly inadequately described (*see* Office Action at 13), is rendered moot by cancelation of claims 33 and 34 with this Amendment. These dependent claims are canceled without prejudice, as discussed above, to expedite prosecution of this application.

B. Definiteness

Similarly, the rejection of claims 39 and 40 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for reciting a "progenitor cell" to a "neural" or "neuronal" cell (*see* Office Action at 11), is rendered moot by cancelation of the claims

at issue. Although the Examiner does not object to the recitation of "neural progenitor cell" in independent claims 27 and 28, Applicants amend these claims to recite a "method for inducing neurite formation from a neuronal cell," to more clearly indicate that the claims encompass "neuronal cells" at all stages of differentiation in the neuronal lineage, but not a "neural progenitor cell" in the glial lineage.

The Examiner also rejects claims 25-34 and 37-40 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite over recitation of "having BMP-11 activity in an osteoinduction assay." In response, Applicants submit that the skilled artisan would readily understand the meaning of this limitation, in view of Applicants' disclosure that one aspect of BMP-11 activity is "the ability to induce the formation of bone, cartilage, and/or other connective tissue" (page 2, lines 25-28). However, to advance prosecution, and without conceding the Examiner's position, Applicants amend the claims to recite a nucleotide sequence that "encodes a protein that promotes the survival of neuronal cells in culture." Support for this limitation, including an exemplary assay for the ability to promote neuronal cell survival, is found at page 45, lines 1-19, for example.

Claims 25-34 and 37-40 are also rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite over recitation of "stringent conditions." Without conceding the Examiner's position, Applicants amend the claims to recite specific hybridization conditions. Support for this limitation is found, e.g., at page 25, lines 15-18.

C. Enablement

The Examiner raises new enablement challenges to claims 25-34 and 37-40 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not reasonably provide enablement for a BMP-11 polypeptide encoded by a nucleotide sequence that hybridizes under stringent conditions with the sequence of part (i) or (ii) of the claims and encodes a protein having BMP-11 activity in an osteoinduction assay. Without conceding the Examiner's position, Applicants have canceled claims 29-34, 37, 39, and 40 and amended claims 25-28 and 38 to require specific stringent conditions comprising hybridizing at 65°C and washing at 65°C in 0.1X SSC, 0.1% SDS. The hybridizing sequences encompassed by amended claims 25-28 also are limited to nucleeotide acid sequences that encode a polypeptide that promotes the survival of neuronal cells in culture. Applicants submit that the amended claims are fully enabled.

Applicants respectfully submit that like dependent claims 35 and 36, new claims 41-52 do not include the hybridization and BMP-11 activity limitations that are the subject of this rejection, and are fully enabled by the specification as filed.

To satisfy the enablement requirement, the specification must enable one skilled in the art to make and use the claimed invention without undue experimentation. *Atlas Powder Co. v. E.I. Du Pont de Nemours*, 750 F.3d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984) ("That some experimentation is necessary does not preclude enablement; the amount of experimentation, however, must not be unduly extensive.") The test considers more than the mere quantity of experimentation. *PPG Industries, Inc. v. Guardian Industries, Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1621 (Fed. Cir. 1996) ("[A] considerable amount of experimentation is permissible, if it is merely

routine"); *see also*, *Ajinomoto Co. v. Archer-Daniels-Midland Co.*, 228 F.3d 1338, 1345, 56 USPQ2d 1332, 1337 (Fed. Cir. 2000) (holding that claims directed to a myriad of bacterial strains not yet known were enabled, where the identification and isolation techniques to discover the strains were well known).

Thus, where, as here, the necessary methods to identify and produce the components for use in the claimed invention are well known and/or routine, the claims are enabled. Hybridization techniques were well known in the art at the time this application was filed.

The Examiner first alleges that because it is unclear if the BMP-11 protein induces or inhibits osteoinduction, neurogenesis, or some other unknown and undescribed activity in an osteoinduction assay, the range of BMP-11 polypeptides having such an activity is not enabled. The Examiner also states that nucleic acid sequences that hybridize to (i) or (ii) are antisense to the coding sequence and therefore do not encode anything remotely resembling the exemplified BMP-11 polypeptides. Applicants note that nucleotide sequences are described in the specification as including double and single-stranded sequences, and that the examiner's rejection is apposite only to single stranded nucleic acids. Nevertheless, to clarify the scope of the nucleotide sequences encompassed by claims 25-28, Applicants have amended part (iii) to remove any apparent ambiguity that might cause the inoperative embodiments to be encompassed by the claims at issue.

The Examiner next alleges that the specification provides no guidance as to which amino acid residues in SEQ ID NO:11 are essential to the structural and functional integrity of the polypeptide nor information regarding which are expendable or

substitutable. The Examiner further states that a skilled artisan would be required to make a substantial inventive contribution to determine which amino acids are required to retain the functional limitation in order to practice the invention, and he states that the specification does not provide the guidance needed to predictably alter the sequence with any reasonable expectation of success.

With these rejections, the Examiner appears to reject the claims for failing to enable an aspect of certain BMP-11 embodiments that is not claimed. Claims 25-28 do not recite 'predictable alteration of the sequence' or 'determination of which amino acids are required to retain function.' It is well established that only the claimed invention must be enabled by the specification, not unclaimed features of the same. *See, e.g., DeGeorge v. Bernier*, 768 F.2d 1318, 1323, 226, USPQ 758, 763 (Fed. Cir. 1985)). *See also, In re Brebner*, 4455 F.2d 1402, 1404, 173 USPQ 169, 171 (CCPA 1972) ("[A] rejection for failure to enable because of failure to disclose how to obtain starting materials [such as the BMP-11 polypeptides at issue here] would be sustainable only if the method of obtaining them would not have been apparent to one of ordinary skill in the art.") Applicants submit that guidance regarding predictable alteration of the sequence is unnecessary because it is not an aspect of the claimed invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.* 857 F.2d 778, 785 (Fed. Cir. 1988). The test for enablement is not whether "any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed" (see Office Action at 12-13), but whether, if experimentation is necessary to practice the

invention, it is undue. *In re Angstadt*, 190 USPQ 214 (CCPA 1976). For example, in *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), the Federal Circuit held that a specification was enabling for claims to antibodies that bind to a specific epitope, where necessary screening and producing methods for making the monoclonal antibodies used in the claimed invention were known. If antibody isolation, screening, and production techniques were well known in the 1970s to 1980s, then surely hybridization procedures would be well known as of the priority date of this application. No undue experimentation would be required to practice the claimed invention because the techniques to make the genus of BMP-11 molecules were known, and the Examiner has not put forward a reasonable basis to question the enablement of the claimed invention (MPEP §2164.04).

As amended, the nucleotide sequences at issue are limited both structurally (a sequence that hybridizes to the nucleotide sequence of (i) or (ii) under the specified hybridization conditions) and functionally (a sequence that encodes a protein that promotes the survival of neuronal cells). The skilled artisan would readily understand how to identify sequences meeting the hybridization limitation. First, the claim recites specific hybridization conditions (hybridizing at 65°C), and the specification includes a detailed protocol for identifying sequences by stringent hybridization (page 24, line 31 to page 26, line 8). Further, such hybridization experiments were well known in the art. See, e.g., Maniatis et al., Molecular Cloning: A Laboratory Manual 387-389 (1982), as cited by Applicants at page 13, lines 31-33.

Having identified a sequence meeting the structural requirement, only routine experimentation would be required to determine whether this sequence also satisfied

the functional limitation. Applicants describe an assay for promoting neuronal cell survival in Example 9 (page 45, lines 1-19). Further, a variety of similar neuronal cell survival assays were routine in the art. *See, e.g.*, Schubert et al., Nature 344:868-870 (1990) and Jordan et al., Eur. J. of Neuroscience 9:1699-1710 (1999), both previously cited by the Examiner. Accordingly, the encompassed nucleotide sequences, namely sequences that meet both the structural and functional requirements, could be identified with only routine experimentation. Applicants thus submit that the amended claims are fully enabled.

The Examiner states that the specification provides no working examples. The claims are amended, however, to relate to methods of promoting the survival of neuronal cells and methods of inducing neurite formation. Both indications are supported by working examples, e.g., at page 45, line 1-19; and page 45, line 29 to page 46, line 3. Further, as noted above, the specification provides exemplary assays for identifying the encompassed sequences and the amended claims require that the nucleotide sequences of part (iii) encode a protein that promotes the survival of neuronal cells in culture. The specification also provides the sequences for bovine and human BMP-11, describes structural and functional similarities with other TGF-β family members, and even lists the percent identity of the C-terminal region of the BMP-11 polypeptide to various other proteins of the TGF- β family (*see, e.g.*, Specification at page 27, lines 24-30).

Further, although the Examiner argues that a reference by Ngo establishes that predicting structure, hence function, from primary amino acid sequence can be complex, the skilled artisan would not expect success in producing sequences that

promote neuronal cell survival in culture, Applicants note that a skilled artisan would not need to predict structure, or develop a structure/function map of any protein to practice the invention.

The standard for enablement is not whether it is possible to "predictably alter the sequence," but whether the skilled artisan could produce, without undue experimentation, sequences that hybridize under the recited conditions to (i) or (ii) and encode a protein that promotes neuronal cell survival in culture. As discussed above, examples of the assays needed to identify sequences meeting both limitations are provided in the specification and were well known in the art. These are far better odds than those at issue in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), in which the court found that screening many hybridomas to find the few that fell within the claims was not undue experimentation. Accordingly, Applicants submit that the skilled artisan could make and use the claimed invention without undue experimentation, and respectfully request that the enablement rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Obviousness-type Double Patenting Rejection

The Examiner continues to reject the pending claims under the judicially created doctrine of obviousness-type double patenting, over U.S. Patent No. 6,340,668, and, if necessary, in view of Wozney (U.S. Patent No. 5,700,911). If the claims as herein amended are deemed otherwise allowable, Applicants will submit a terminal disclaimer in this application. However, until such allowable subject matter is agreed upon, Applicants respectfully maintain that terminal disclaimer of the term of any patent that may issue from this application is premature. Although the Examiner states that there

are no provisions for holding a rejection in abeyance, it is well-established practice to allow an Applicant to delay submission of a terminal disclaimer to overcome a provisional obviousness-type double patenting rejection until otherwise allowable subject matter is identified.

Conclusion

Applicant submit that with this amendment, claims 25-28, 35, 36, and 41-52 are in condition for allowance. Applicants submit that the proposed amendments of claims 25-28, 35 and 36 and the addition of claims 41-52 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06 0916.

Respectfully submitted,

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Dated: September 19, 2005

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